Brexpiprazole Tablets

(Rexulti®)

Classification: Atypical Antipsychotic Agent

Pharmacology:

The mechanism of action of brexpiprazole in the treatment of major depressive disorder or schizophrenia is unknown. However, the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors.

Pharmacokinetics:

Absorption: After single dose administration of brexpiprazole tablets, the peak plasma concentrations occurred within 4 hours after administration, with an absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10-12 days of dosing. It can be administered with or without food.

Distribution: Brexpiprazole is highly protein bound in plasma (greater than 99%) to serum albumin and α1-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment.

Metabolism: Metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6. Brexpiprazole and its major metabolite DM-3411 are the predominant drug moieties in the systemic circulation, though DM-3411 is not considered to contribute to therapeutic effect.

Elimination: After multiple once daily administrations, the terminal elimination half-lives of brexpiprazole and its major metabolite, DM-3411, were 91 hours and 86 hours, respectively.

Indications:

Brexpiprazole is indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) and for the treatment of schizophrenia (SCZ).

Dosage and Administration:

MDD: The starting dose is 0.5-1 mg/day, with a recommended dose of 2 mg/day and a maximum dose of 3 mg/day.
SCZ: The starting dose is 1 mg/day, with a recommended dose of 2-4 mg/day and a maximum dose of 4 mg/day.

In moderate to severe hepatic impairment (Child-Pugh score ≥7): The maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia.
In moderate, severe or end-stage renal impairment (ClCr < 60 mL/minute): The maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with SCZ.

Interactions:

- In strong CYP2D6 **or** CYP3A4 inhibitors, administer half of usual dose. Dosage adjustment may not be needed with strong CYP2D6 inhibitors in patients with MDD.
- In strong/moderate CYP2D6 with strong/moderate CYP3A4 inhibitors, administer a quarter of usual dose.
- In known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors, administer a quarter of usual dose.
- In strong CYP3A4 inducers, double the usual dose and further adjust based on clinical response.

Precautions:

- Cerebrovascular adverse reactions and increased mortality in elderly patients with dementia related psychosis
- Dysphagia
- Neuroleptic Malignant Syndrome
- Body Temperature Dysregulation
- Tardive Dyskinesia
- Cognitive and Motor Impairment
    - Higher rates of sedation and hypersomnia were reported with brexpiprazole compared to placebo in MDD and SCZ trials (MDD 4% vs. 1%; SCZ 5% vs. 3%)
- Metabolic Changes:
    - Hyperglycemia/diabetes mellitus- There have been reports of weight gain and hyperglycemia in patients treated with brexpiprazole. Proportions of patients experiencing a shift from normal or borderline to high glucose (≥126 mg/dL) were similar in short-term, 6-week trials between placebo and brexpiprazole. During the long-term, open-label trials 9% of subjects in the MDD studies experienced shifts in glucose from normal or borderline to high and 10% of subjects in the SCZ long-term, open-label experienced shifts in glucose from normal or borderline to high.

    - Lipids- In the short-term, 6-week trials in MDD and SCZ changes between total cholesterol, LDL and HDL were similar between brexpiprazole and placebo; however, increases in triglycerides ≥ 200 mg/dL were more commonly seen with brexpiprazole than placebo (brexpiprazole range depending on dose and population 5-13%, placebo 6%). In the long-term studies shifts from normal to high were reported for total cholesterol (MDD 9%, SCZ 6%), LDL (MDD 3%, SCZ 2%), HDL (MDD 14%, SCZ 17%) and triglycerides (MDD 17%, SCZ 13%). Infrequently shifts in triglycerides from normal or borderline to very high (≥ 500 mg/dL) were seen in the combined MDD or SCZ groups 0.6%.
    - Weight- In the MDD trials, brexpiprazole was associated with a mean change from baseline in weight of 2.9 kg at 26 weeks and 3.1 kg at 52 weeks. In the SCZ trials, brexpiprazole was associated with a mean change from baseline in weight of 1.3 kg at 26 weeks and 2.0 kg at 52 weeks.
- Leukopenia, neutropenia, and agranulocytosis
- Orthostatic Hypotension (MDD 0.1%, SCZ 0.4%) and Syncope (SCZ 0.1%)
- Seizures
- Suicidal thoughts or behaviors in children and young adults
- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure

Adverse Reactions:

Most common adverse reactions in MDD (≥5% and at least twice the rate for placebo): Increased weight and akathisia (9% brexpiprazole vs. 2% placebo). Incidence of akathisia increased with higher dosages.

Most common adverse reactions in Schizophrenia: Increased weight (≥4% and at least twice the rate for placebo).

- Akathisia was seen less frequently in the SCZ group (6% brexpiprazole vs. 5% placebo) than the MDD group noted above.

Cost Comparison:

Pricing information for brexpiprazole; it is flat price $28.85 per tablet acquisition cost for all strengths (0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, up to 4 mg) and it is not available in unit dose at this time so it would need to be UD packaged in house (extra $ time/supplies) for inpatient use.

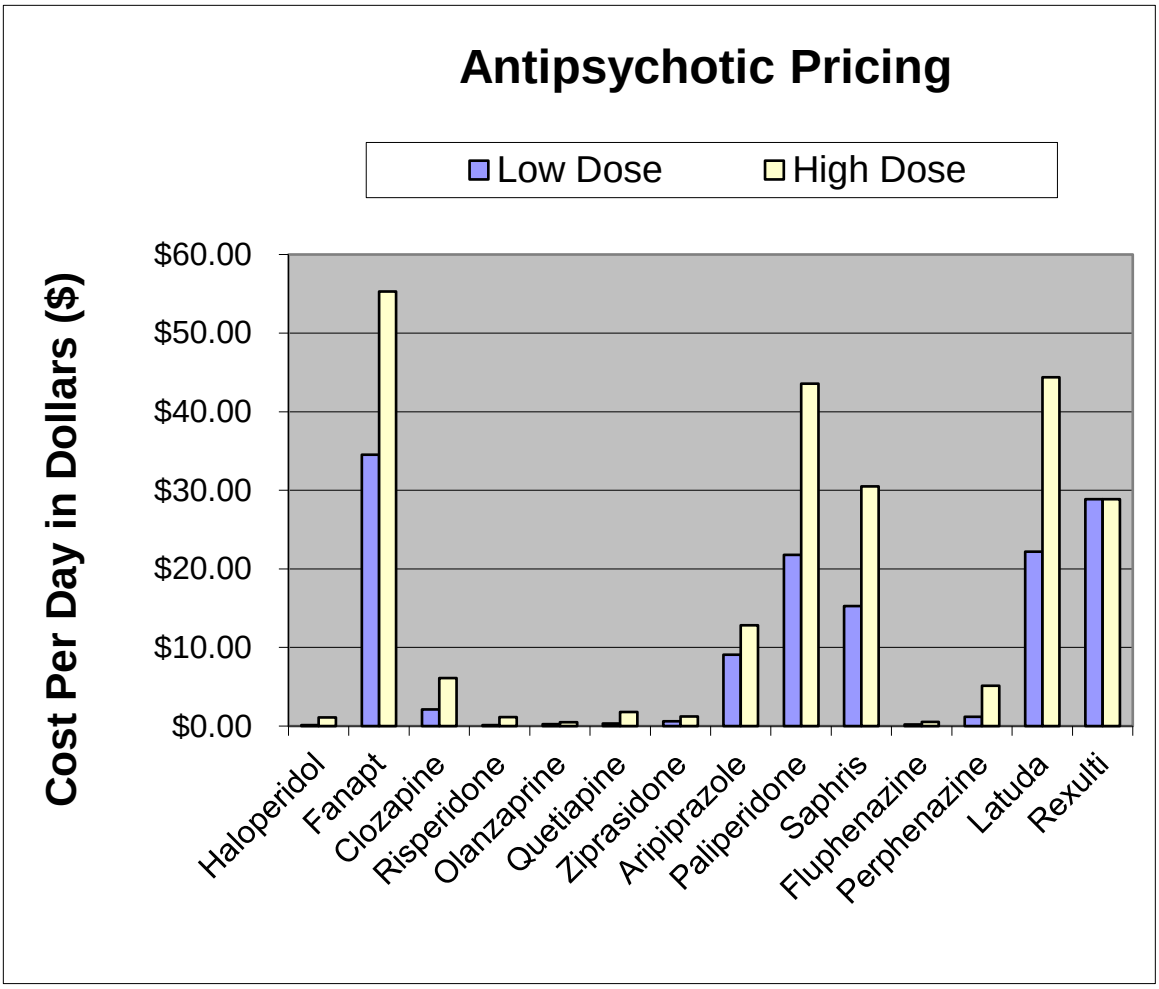
Monitoring:

Recommend same as current DSHS EFC monitoring requirements for atypical antipsychotics:

1) Pregnancy test – as clinically indicated

2) BMI and waist circumference measurement – when a new antipsychotic is initiated, at every visit (monthly for inpatients) for 6 months after the new antipsychotic is initiated, and quarterly when the antipsychotic dose is stable
3) Fasting plasma glucose level or hemoglobin A1c – before initiating a new antipsychotic, then yearly. If a patient has significant risk factors for diabetes and for those that are gaining weight – before initiating a new antipsychotic, 4 months after starting an antipsychotic, and then yearly
4) Lipid screening [total cholesterol, low- and high-density lipoprotein (LDL and HDL) cholesterol, and triglycerides] – Every 2 years or more often if lipid levels are in the normal range, every 6 months if the LDL level is > 130 mg/dl
6) Sexual function inquiry – inquire for evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory disturbance yearly
If a patient is receiving an antipsychotic known to be associated with prolactin elevation, then at each visit (quarterly for inpatients) for the first 12 months after starting an antipsychotic or until the medication dose is stable and then yearly
7) Prolactin level – if there is evidence of galactorrhea/gynecomastia, menstrual disturbance, libido disturbance or erectile/ejaculatory yearly
8) EPS Evaluation (examination for rigidity, tremor, akathisia) – before initiation of any antipsychotic medication, then weekly for the first 2 weeks after initiating treatment with a new antipsychotic or until the dose has been stabilized and weekly for 2 weeks after a dose increase
9) Tardive dyskinesia evaluation – every 3 months and as clinically indicated
10) Vision questionnaire – ask whether the patient has experienced a change in vision and should specifically ask about distance vision and blurry vision – yearly
11) Ocular evaluations – yearly for patients older than age 40 years; every 2 years for younger patients

Figure 1. Antipsychotic Pricing



Product Identification:
0.25 mg tablets: light brown, round, shallow convex; bevel-edged with markings "BRX" and "0.25"
0.5 mg tablets: light orange, round, shallow convex; bevel-edged with markings "BRX" and "0.5"
1 mg tablets: light yellow, round, shallow convex; bevel-edged with markings "BRX" and "1"
2 mg tablets: light green, round, shallow convex; bevel-edged with markings "BRX" and "2"
3 mg tablets: light purple, round, shallow convex; bevel-edged with markings "BRX" and "3"
4 mg tablets: white, round, shallow convex; bevel-edged with markings "BRX" and "4"

Efficacy:

Schizophrenia: Two six week, randomized, double-blind, placebo-controlled trial demonstrated efficacy of brexpiprazole in schizophrenia[1,2]. Patients included in the studies were between the ages of 18 and 65 years of age who had a diagnosis of schizophrenia as defined by DSM IV and were experiencing an acute exacerbation of psychotic symptoms. There was a required washout period of 3 to 28 days for all psychotropic medications, including antipsychotics, antidepressants, mood stabilizers, and benzodiazepines. Participants were randomized 2:3:3:3 into 1, 2, or 4 mg brexpiprazole, or placebo and hospitalized throughout the screening and treatment period. Patients were assessed weekly and followed up for safety for 30 days after the last dose of the medication.

The primary endpoint was a mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score and the key secondary outcome was a mean change from baseline to week 6 in Clinical Global Impression-Severity (CGI-S) score. Data analysis was based on three populations: randomized, safety, and efficacy. The randomized samples included all patients randomized to treatment during the trial. Safety samples included randomized participants that had received at least one dose of the trial medication. Efficacy populations included the safety samples who had at least one baseline and post-baseline efficacy measurement. The primary endpoint (PANSS total score) was analyzed using a mixed model for repeated measures (MMRM) analysis. Differences of the average effect were tested at a significance level of 0.05. If the results were significant, a comparison of each 2 mg and 4 mg dose with placebo was tested. If those results were significant, a comparison of the key secondary endpoint (CGI-S score) was used at a significance level of 0.05.

In the first study[1], the average effect of brexpiprazole compared to placebo was a least squares mean difference of -4.78 (p = 0.0093). Individual doses of brexpiprazole showed a statistically significant reduced PANSS Total Score for only brexpiprazole 4 mg compared to placebo (-6.47 treatment difference, p = 0.0022). Brexpiprazole 4 mg showed statistically significant improvement compared with placebo in the CGI-S score at week 6, with a treatment difference of -0.38 (p = 0.0015). In the second study[2], brexpiprazole at both 2 mg/day and 4 mg/day was superior to placebo on the PANSS total score, which is displayed in figure 2.

Table 1. Primary Efficacy in Schizophrenia

Study	Treatment Group	N	Primary Efficacy Measure: MADRS		
			Mean Baseline Score	Least Squares Mean Change from baseline	Placebo-subtracted

					Difference (95% CI)
1	Brexpiprazole 2 mg/day	180	95.9 (13.8)	-20.7 (1.5)	-8.7 (13.1, -4.4)
1	Brexpiprazole 4 mg/day	178	94.7 (12.06)	-19.7 (1.54)	-7.6 (-12.0, -3.1)
1	Placebo	178	95.7 (11.5)	-12.0 (1.6)	--
2	Brexpiprazole 2 mg/day	179	96.3 (12.9)	-16.6 (1.5)	-3.1 (-7.2, 1.1)
2	Brexpiprazole 4 mg/day	181	95.0 (12.4)	-20.0 (1.5)	-6.5 (-10.6, -2.4)
2	Placebo	180	94.6 (12.8)	-13.5 (1.5)	--

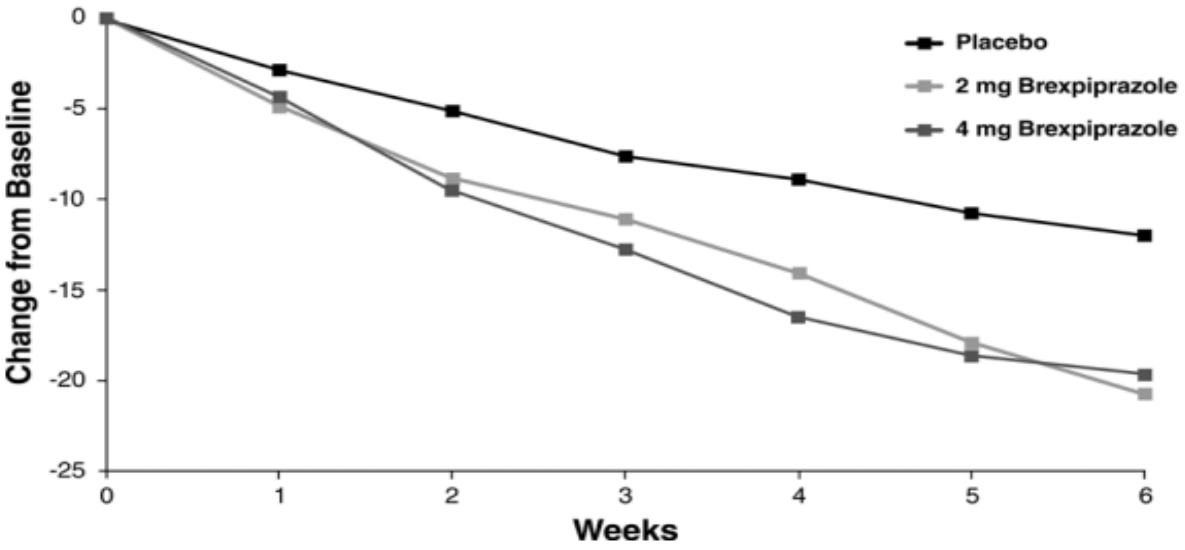


Figure 2. Change in MADRS score from baseline in SCZ[2]

There were no common adverse events, defined as greater than 5% in brexpiprazole groups and greater than 2 times the placebo rate[1]. Table 2 shows the common treatment-emergent adverse events for any group. Akathisia was reported less frequently in the brexpiprazole treatment groups than in placebo. There was more weight gain in brexpiprazole-treated patients (LS mean gain: 1.23 kg [1 mg], 1.89 kg [2 mg], 1.52 kg [4 mg]) than placebo-treated patients (LS mean gain 0.35 kg). Changes in creatine phosphokinase levels (≥ 3x ULN) were also higher in the

brexpiprazole treatment groups (7.7% [1 mg], 9.6% [2 mg], 8.0% [4 mg]) than in placebo (4.2%).

Table 2. Treatment-emergent adverse events in ≥ 5% of patients in any group, n(%)[1]

TEAE	Placebo (n = 184)	Brexpiprazole 1 mg (n = 120)	Brexpiprazole 2 mg (n = 186)	Brexpiprazole 4 mg (n = 184)
At least 1 TEAE	102 (55.4)	68 (56.7)	109 (58.6)	119 (63.0)
Discontinuation due to TEAE	22 (12.0)	11 (9.2)	11 (5.9)	13 (7.1)
Akathisia	13 (7.1)	5 (4.2)	9 (4.8)	12 (6.5)
Agitation	13 (7.1)	10 (8.3)	16 (8.6)	13 (7.1)
Dyspepsia	6 (3.3)	7 (5.8)	7 (3.8)	6 (3.3)
Headache	27 (14.7)	9 (7.5)	20 (10.8)	19 (10.3)
Insomnia	27 (14.7)	15 (12.5)	25 (13.4)	28 (15.2)
Schizophrenia	18 (9.8)	4 (3.3)	8 (4.3)	10 (5.4)

Adjunctive agent in MDD: The efficacy of brexpiprazole in the adjunctive treatment of major depressive disorder (MDD) was evaluated in two 6-week, double-blind, placebo-controlled, fixed-dose trials of adult patients meeting DSM-IV-TR criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response throughout the 8 weeks of prospective antidepressant treatment (with escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed release, or venlafaxine extended-release)[3,4]. Inadequate response during the prospective antidepressant treatment phase was defined as having persistent symptoms without substantial improvement throughout the course of treatment. Patients were randomized to brexpiprazole 1, 2, or 3 mg once a day or placebo. For patients randomized to brexpiprazole, all patients initiated treatment at 0.5 mg once daily during Week 1. At Week 2, the

dosage was increased to 1 mg in all treatment groups, and either maintained at 1 mg or increased to 2 mg or 3 mg once daily, based on treatment assignment, from Week 3 onwards. The dosages were then maintained for the 4 remaining weeks. The primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms, and 60 representing worst symptoms. At randomization, the mean MADRS total score was 27. Brexpiprazole (+ antidepressant (ADT)) 2 mg/day and 3 mg/day were superior to placebo + ADT in reducing mean MADRS total scores. Results from the primary efficacy parameters for both fixed dose trials are shown below in Table 3. Figure 3 below shows the time course of response based on the primary efficacy measure (MADRS).

Table 3. Primary Efficacy in MDD

Study	Treatment group	N	Primary Efficacy Measure: MADRS		
			Mean Baseline Score	Least Squares Mean Change from baseline	Placebo-subtracted Difference (95% CI)
3	Brexpiprazole (2 mg/day) + ADT	175	26.9 (±5.7)	-8.4 (±0.6)	-3.2 (-4.9, -1.5)
3	Placebo + ADT	178	27.3 (±5.6)	-5.2 (±0.6)	--
4	Brexpiprazole (1 mg/day) + ADT	211	36.5 (±5.6)	-7.6 (±0.5)	-1.3 (-2.7, 0.13)
4	Brexpiprazole (3 mg/day) + ADT	213	26.5 (±5.3)	-8.3 (±0.5)	-2.0 (-3.4, -0.5)
4	Placebo + ADT	203	26.5 (±5.2)	-6.3 (±0.5)	--

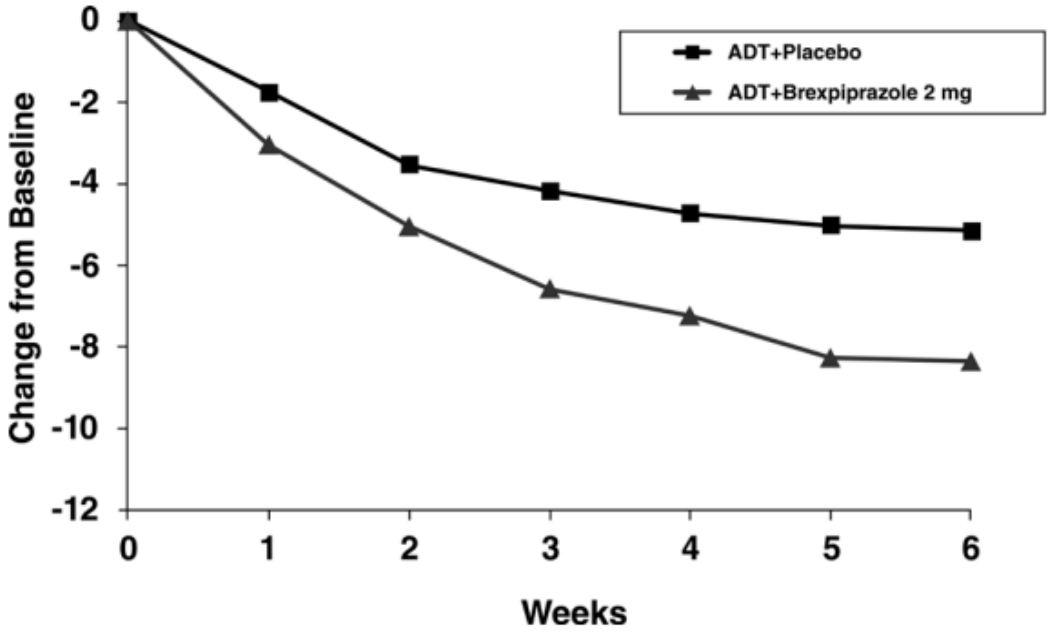


Figure 3. Change in MADRS score from baseline in MDD[3]

Conclusion:
Brexpiprazole has shown efficacy over placebo in both trials as an adjunctive agent in MDD at doses of 1-3 mg[3,4]. It also displayed a significant improvement in PANSS score in SCZ at 4 mg in the first study[1], and at 2-4 mg in the second study[2]. In terms of side effects, there is a low risk of EPS, sedation, orthostasis and QT prolongation, though a >5% risk of weight gain in both MDD and SCZ and a risk >5% risk of akathisia in MDD that were displayed in the trials. From a cost perspective it is comparable to some of the other newer antipsychotics at ~$28.85/day at all doses.

Recommendation:
Recommended for addition to the formulary.

References:

1. Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophr Res. 2015 May;164(1-3):127-35.

2. Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuare RD, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry. 2015 Sep 1;172(9):870-80.

3. Thase ME, Youakim JM, Skuban A, Hobart A, Augustine C, Zhang P, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015 Sep;76(9):1224-31.

4. Thase ME, Youakim JM, Skuban A, Hobart A, Augustine C, Zhang P, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. J Clin Psychiatry. 2015 Sep;76(9):1232-40.

5. Rexulti® (brexpiprazole) [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc. July 2015.

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